AMENDMENT

It is respectfully requested that the application be amended without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents, as follows.

IN THE CLAIMS

Please amend the claims, as follows, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents:

56. (Amended) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self-protein, by containing a substitution of a peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, wherein the peptide fragment corresponds to the peptide containing at least one immunodominant T-cell epitope in amino acid length;

whereby, the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

57. (Amended) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self-protein, by containing a substitution of a peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, wherein the substitution is of an alpha-helix;

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

58. (Amended) The method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, according to claim 57 wherein the alpha helix is an amphiphatic alpha helix.

59. (Amended) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self-protein, by containing a substitution of a peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, wherein the peptide fragment corresponds to the peptide containing at least one immunodominant T-cell epitope in amino acid length and comprises at least ten amino acids;

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

60. (Amended) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self-protein, by containing a substitution of a peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, wherein the peptide fragment corresponds to the peptide containing at least one immunodominant T-cell epitope in amino acid length and comprises at least fifteen amino acids,

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

61. (Amended) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self-protein, by containing a substitution of a peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

whereby the modified self-protein elicits antibodies that are against the self-protein; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken.

62. (Amended) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self-protein, by being detoxified by containing a substitution of a peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

63. (Amended) The method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, of claim 56 wherein the substitution preserves flanking regions comprising at least four amino acids on each side of the peptide fragment.

64. (Amended) The method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, of claim 59 wherein the substitution preserves flanking regions comprising at least four amino acids on each side of the peptide fragment.

65. (Amended) The method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, of claim 60 wherein the substitution preserves flanking regions comprising at least four amino acids on each side of the peptide fragment.

66. (Amended) The method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal of claim 62 wherein the peptide fragment corresponds to the peptide containing at least one immunodominant T-cell epitope in amino acid length.

67. (Amended) The method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal of claim 66 wherein the T-cell epitope comprises at least 10 amino acids.

68. (Amended) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising;

preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self-protein, by containing a substitution of a peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

69. (Amended) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising;

preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self-protein, by containing a substitution of a peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken, wherein:

the peptide containing at least one immunodominant T-cell epitope comprises at least 15 amino acids.

70. (Amended) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

a. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self-protein, by containing a substitution of a peptide fragment of the self-protein with a peptide containing at

least one immunodominant T-cell epitope which is foreign to the animal, wherein the peptide fragment corresponds to the peptide containing at least one immunodominant T-cell epitope in amino acid length;

whereby, the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

b. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self-protein, by containing a substitution of a peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, wherein the substitution is of an amphiphatic alpha helix;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

c. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self-protein, by containing a substitution of a peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, wherein the peptide fragment corresponds to the peptide containing at least one immunodominant T-cell epitope in amino acid length and comprises at least ten amino acids;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

d. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self-protein, by containing a substitution of a peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, wherein the peptide fragment corresponds to the peptide containing at least one immunodominant T-cell epitope in amino acid length and comprises at least fifteen amino acids;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

e. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self-protein, by containing a substitution of a peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, wherein the peptide fragment corresponds to the peptide containing at least one immunodominant T-cell epitope in amino acid length and comprises at least 10 amino acids with said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

f. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self-protein, by containing a substitution of a peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, wherein the peptide fragment corresponds to the peptide containing at least one immunodominant T-cell epitope in amino acid length and comprises at least 15 amino acids with said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein earlier and in higher titres, in comparison to the self-protein conjugated to a carrier

protein or peptide containing T-cell epitopes; and B-cell autotolerance to the self-protein is broken; or,

g. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self-protein, by being detoxified by containing a substitution of a peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

h. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self-protein, by being detoxified by containing a substitution of a peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, and said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

i. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self-protein, by being detoxified by containing a substitution of a peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, wherein said peptide containing at least one immunodominant T-cell epitope comprises at least 10 amino acids and said substitution preserves flanking regions comprising at least four amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

j. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self-protein, by being detoxified by containing a substitution of a peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, wherein the peptide containing at least one immunodominant T-cell epitope comprises at least 15 amino acids and said substitution preserves flanking regions comprising at least four amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken.

71. (Amended) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, inducing antibody production in the animal against the self-protein of that animal, and eliciting an immune response in the animal which includes an MHC class II immune response as to an immunodominant T-cell epitope which is foreign to the animal and an autoantibody response in other MHC-haplotypes, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self-protein, by containing a substitution of a peptide fragment of the self-protein with a peptide containing the immunodominant T-cell epitope which is foreign to the animal,

whereby the modified self-protein elicits antibodies that are against the self-protein; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken.

73. (Amended) The method of any one of claims 56-71 wherein the modified self-protein is a recombinant modified self-protein.

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74. (Amended) The method of any one of claims 56-71 wherein the self-protein is tumor necrosis factor alpha (TNF-α), tumor necrosis factor beta (TNF-β), gamma interferon (γ-interferon), interleukin 1 (IL-1) or immune globulin (IgE).

75. (Not Amended) The method of claim 73 wherein the self-protein is tumor necrosis factor alpha (TNF-α), tumor necrosis factor beta (TNF-β), gamma interferon (γ-interferon), interleukin 1 (IL-1) or immune globulin (IgE).

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76. (Amended) The method of any one of claims 56-71 wherein the administering includes administering an adjuvant.

77. (Not Amended) The method of claim 76 wherein the adjuvant comprises calcium phosphate, saponin, quil A or a biodegradable polymer.

78. (Not Amended) The method of claim 73 wherein the administering includes an adjuvant.

79. (Not Amended) The method of claim 75 wherein the administering includes an adjuvant.

Please add the following new claims, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents:

--80. (New) The method of claim 79 wherein the self-protein is tumor necrosis factor alpha (TNF-α).

81. (New) The method of claim 79 wherein the self-protein is tumor necrosis factor beta (TNF-β).

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82. (New) The method of claim 79 wherein the self-protein is gamma interferon (γ-interferon).

83. (New) The method of claim 79 wherein the self-protein is interleukin 1 (IL-1).

84. (New) The method of claim 79 wherein the self-protein is immune globulin (IgE).--

Please cancel claim 72, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents.